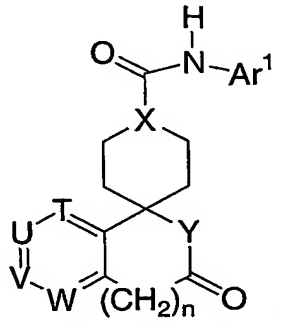
WHAT IS CLAIMED IS:

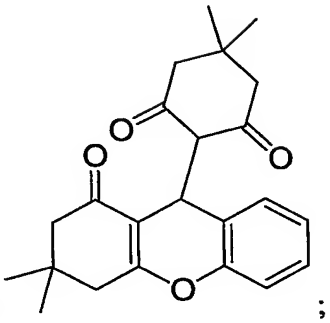
1. A composition comprising

(a) a NPY5 antagonist of formula I or II



(I)

or



;

(II)

and pharmaceutically acceptable salts and esters thereof, wherein

Ar^1 is selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein the aryl and heteroaryl groups are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,

(b) nitro,

(c) lower alkyl,

(d) halo(lower)alkyl,

(e) hydroxy(lower)alkyl,

(f) cyclo(lower)alkyl,

(g) lower alkenyl,

(h) lower alkoxy,

(i) halo(lower)alkoxy,

(j) lower alkylthio,

(k) carboxyl,

(l) lower alkanoyl,
(m) lower alkoxycarbonyl,
(n) lower alkylene optionally substituted with oxo, and
(o) -Q-Ar^2;

Ar^2 is selected from the group consisting of
(1) aryl, and
(2) heteroaryl,
wherein aryl and heteroaryl are unsubstituted or optionally substituted with a substituent selected from the group consisting of:
(a) halogen,
(b) cyano,
(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) hydroxy,
(g) lower alkoxy,
(h) halo(lower)alkoxy,
(i) lower alkylamino,
(j) di-lower alkylamino,
(k) lower alkanoyl, and
(l) aryl;

n is 0 or 1;
Q is selected from the group consisting of a single bond or carbonyl;
T, U, V and W are each independently selected from the group consisting of
(1) nitrogen, and
(2) methine,
wherein the methine group is unsubstituted or optionally substituted with a substituent selected from the group consisting of
(a) halogen,
(b) lower alkyl,
(c) hydroxy, and
(d) lower alkoxy, and
wherein at least two of T, U, V, and W are methine;
X is selected from the group consisting of

(1) nitrogen, and

(2) methine; and

Y is selected from the group consisting of

(1) imino, unsubstituted or optionally substituted with lower alkyl, and

(2) oxygen; and

(b) an antiobesity agent selected from the group consisting of:

(1) 5HT transporter inhibitor;

(2) NE transporter inhibitor;

(3) CB-1 antagonist/inverse agonist;

(4) Ghrelin antagonist;

(5) H3 antagonist/inverse agonist;

(6) MCH1R antagonist;

(7) MCH2R agonist/antagonist;

(8) NPY1 antagonist;

(9) leptin;

(10) leptin derivatives;

(11) opioid antagonist;

(12) orexin antagonist;

(13) BRS3 agonist;

(14) CCK-A agonist;

(15) CNTF;

(16) CNTF derivatives;

(17) GHS agonist;

(18) 5HT2C agonist;

(19) monoamine reuptake inhibitor;

(20) UCP-1, 2, and 3 activator;

(21) β3 agonist;

(22) thyroid hormone β agonist;

(23) PDE inhibitor;

(24) FAS inhibitor;

(25) DGAT1 inhibitor;

(26) DGAT2 inhibitor;

(27) ACC2 inhibitor;

(28) glucocorticoid antagonist;

(29) acyl-estrogens;
(30) lipase inhibitor;
(31) fatty acid transporter inhibitor;
(32) dicarboxylate transporter inhibitor;
(33) glucose transporter inhibitor;
(34) serotonin reuptake inhibitors;
(35) metformin; and
(36) topiramate;

and pharmaceutically acceptable salts and esters thereof.

2. The composition of Claim 1 wherein the anti-obesity agent is selected from the group consisting of:

(1) acyl-estrogen;
(2) CB-1 antagonist/inverse agonist;
(3) opioid antagonist;
(4) monoamine reuptake inhibitor;
(5) lipase inhibitor;
(6) leptin;
(7) CNTF;
(8) CNTF derivatives;
(9) metformin; and
(10) topiramate;

and pharmaceutically acceptable salts and esters thereof.

3. The composition of Claim 2 wherein the acyl-estrogen is selected from oleoyl-estrone, and the pharmaceutically acceptable salts thereof.

4. The composition of Claim 2 wherein the monoamine reuptake inhibitor is selected from sibutramine, and the pharmaceutically acceptable salts thereof.

5. The composition of Claim 2 wherein the CNTF derivative is selected from axokine, and the pharmaceutically acceptable salts thereof.

6. The composition of Claim 2 wherein the lipase inhibitor is selected from orlistat, and the pharmaceutically acceptable salts thereof.

7. The composition of Claim 2 wherein the CB-1 antagonist/inverse agonist is selected from rimonabant, and the pharmaceutically acceptable salts thereof.

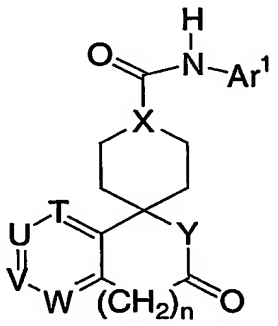
8. The composition of Claim 2 wherein the anti-obesity agent is selected from leptin, and the pharmaceutically acceptable salts thereof.

9. The composition of Claim 2 wherein the opioid antagonist is selected from nalmefene, and the pharmaceutically acceptable salts thereof.

10. The composition of Claim 2 wherein the anti-obesity agent is selected from topiramate, and the pharmaceutically acceptable salts thereof.

11. The composition of Claim 2 wherein the anti-obesity agent is selected from metformin, and the pharmaceutically acceptable salts thereof.

12. The composition of Claim 1 wherein the NPY5 antagonist is selected from the group consisting of a compound of formula I



(I)

and pharmaceutically acceptable salts and esters thereof, wherein Ar^1 is selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein the aryl and heteroaryl groups are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,

(b) nitro,

(c) lower alkyl,

(d) halo(lower)alkyl,

(e) hydroxy(lower)alkyl,

(f) cyclo(lower)alkyl,

(g) lower alkenyl,

(h) lower alkoxy,

(i) halo(lower)alkoxy,

(j) lower alkylthio,

(k) carboxyl,

(l) lower alkanoyl,

(m) lower alkoxycarbonyl,

(n) lower alkylene optionally substituted with oxo, and

(o) -Q-Ar^2;

Ar^2 is selected from the group consisting of

(1) aryl, and

(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,

(b) cyano,

(c) lower alkyl,

(d) halo(lower)alkyl,

(e) hydroxy(lower)alkyl,

(f) hydroxy,

(g) lower alkoxy,

(h) halo(lower)alkoxy,

(i) lower alkylamino,

(j) di-lower alkylamino,

(k) lower alkanoyl, and

(l) aryl;

n is 0 or 1;

Q is selected from the group consisting of a single bond or carbonyl;

T, U, V and W are each independently selected from the group consisting of

(1) nitrogen, and

(2) methine,

wherein the methine group is unsubstituted or optionally substituted with a substituent selected from the group consisting of

(a) halogen,

(b) lower alkyl,

(c) hydroxy, and

(d) lower alkoxy; and

wherein at least two of T, U, V, and W are methine;

X is selected from the group consisting of

(1) nitrogen, and

(2) methine; and

Y is selected from the group consisting of

(1) imino, unsubstituted or optionally substituted with lower alkyl, and

(2) oxygen.

13. The composition of Claim 12 wherein the NPY5 antagonist is selected from the group consisting of:

(1) N-(4-benzoylphenyl)-3-oxospiro[isoindoline-1,4'-piperidine]-1'-carboxamide;

(2) 3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[isoindoline-1,4'-piperidine]-1'-carboxamide;

(3) N-(7-methyl-2-quinolyl)-3-oxospiro[isoindoline-1,4'-piperidine]-1'-carboxamide;

(4) N-(4-benzoylphenyl)-2-methyl-3-oxospiro[isoindoline-1,4'-piperidine]-1'-carboxamide;

(5) N-(4-benzoylphenyl)-3,4-dihydro-3-oxospiro[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(6) 3,4-dihydro-3-oxo-N-(5-phenyl-2pyrazinyl)spiro-[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(7) 3,4-dihydro-N-(7-methyl-2-quinolyl)-3-oxospiro-[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(8) N-(4-acetylphenyl)-3,4-dihydro-3-oxospiro-[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(9) 3,4-dihydro-3-oxo-N-[1-(2-quinolyl)-4-imidazolyl]-spiro[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(10) 3,4-dihydro-3-oxo-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthyl)spiro[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(11) 3,4-dihydro-N-[5-(2-methyl-1-propenyl)-2-pyrazinyl]-3-oxospiro[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(12) 3,4-dihydro-3-oxo-N-(3-phenyl-5-isoxazolyl)spiro-[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(13) N-[1-(7-benzo[b]furanyl)-4-imidazolyl]-3,4-dihydro-3-oxospiro[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(14) N-[1-(3-difluoromethoxyphenyl)-4-imidazolyl]-3,4-dihydro-3-oxospiro[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(15) 3,4-dihydro-3-oxo-N-[4-(2-pyridylcarbonyl)phenyl]-spiro[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(16) N-(3,4-dichlorophenyl)-3,4-dihydro-3-oxospiro- [isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(17) N-[1-(3-chlorophenyl)-4-imidazolyl]-3,4-dihydro-3-oxospiro[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(18) 3,4-dihydro-3-oxo-N-(5-phenyl-2-thiazolyl)spiro-[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(19) 3,4-dihydro-3-oxo-N-[5-(2-pyridyl)-2-pyrazinyl]spiro-[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(20) 3,4-dihydro-N-(4-methyl-2-benzothiazolyl)-3-oxospiro-[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(21) N-(5-chloro-2-benzoxazolyl)-3,4-dihydro-3-oxospiro-[isoquinoline-1(2H),4'-piperidine]-1'-carboxamide;

(22) N-(4-benzoylphenyl)-3-oxospiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(23) 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(24) N-(7-methyl-2-quinolyl)-3-oxospiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(25) 3-oxo-N-(3-phenyl-5-isoxazolyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(26) 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(27) 3-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(28) 3-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(29) 3-oxo-N-(5-phenyl-3-pyrazolyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(30) N-[5-(4-chlorophenyl)-3-pyrazolyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(31) 3-oxo-N-[5-(3-quinolyl)-3-pyrazolyl]spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(32) N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(33) 3-oxo-N-[5-(3-trifluoromethylphenyl)-2-pyrimidinyl]-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(34) N-[5-(3-chlorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(35) N-(7-difluoromethoxypyrido[3,2-b]pyridin-2-yl)-3-oxospiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(36) 3-oxo-N-(5-phenyl-1,2,4-thiadiazol-3-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(37) N-{1-[3-(2-hydroxyethyl)phenyl]-4-imidazoly}-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(38) N-[4-(1-ethyl-2-imidazolyl)phenyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(39) N-[1-(3-methoxyphenyl)-4-imidazolyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(40) 6-fluoro-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(41) 6-fluoro-3-oxo-N-(5-phenyl-2-pyrimidinyl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(42) 5-fluoro-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(43) 5-fluoro-3-oxo-N-(5-phenyl-2-pyrimidinyl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(44) N-(4-benzoylphenyl)-3,4-dihydro-3-oxospiro[1H-2-benzopyran-1,4'-piperidine]-1'-carboxamide;

(45) 3,4-dihydro-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[1H-2-benzopyran-1,4'-piperidine]-1'-carboxamide;

(46) N-(5-benzoyl-2-pyrazinyl)-3,4-dihydro-3-oxospiro[1H-2-benzopyran-1,4'-piperidine]-1'-carboxamide;

(47) trans-N-(4-benzoylphenyl)-3'-oxospiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(48) trans-3'-oxo-N-(5-phenyl-2-pyrazinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(49) trans-3'-oxo-N-(1-phenyl-4-imidazolyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(50) trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(51) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3'-oxospiro-[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(52) trans-3'-oxo-N-(5-phenyl-3-pyrazolyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(53) trans-N-[1-(2-fluorophenyl)-4-imidazolyl]-3'-oxospiro-[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(54) trans-N-(4-acetyl-3-trifluoromethylphenyl)-3'-oxospiro-[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(55) trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]-spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(56) trans-N-[1-(3-cyanophenyl)-4-imidazolyl]-3'-oxospiro-[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(57) trans-N-(4-benzoylphenyl)-3-oxospiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(58) trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(59) trans-3-oxo-N-(3-phenyl-5-isoxazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(60) trans-3-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(61) trans-N-(4-benzoylphenyl)-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(62) trans-N-(4-benzoylphenyl)-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(63) N-[5-(4-hydroxyphenyl)-2-pyrazinyl]-3-oxospiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(64) N-[5-(3-hydroxyphenyl)-2-pyrazinyl]-3-oxospiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(65) 4-fluoro-3-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(66) 7-fluoro-3-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(67) 6-ethyl-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(68) 6-hydroxy-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(69) trans-3-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(70) trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(71) trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(72) trans-3-oxo-N-(4-phenyl-2-oxazolyl)spiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(73) trans-N-[5-(2-methylphenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(74) trans-N-[5-(3-methylphenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(75) trans-N-[5-(3-fluoromethoxyphenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(76) trans-N-[5-(3-fluoromethylphenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(77) trans-N-[5-(3-fluoro-5-methoxyphenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(78) trans-N-[5-(2-fluoro-5-methylphenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(79) trans-N-[4-(3-fluoromethoxyphenyl)-2-oxazolyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(80) trans-N-[5-(3-hydroxymethylphenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(81) trans-N-[5-(3-hydroxyphenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(82) trans-3-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(83) trans-N-[5-(3-fluoromethylphenyl)-2-pyrimidinyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(84) trans-N-[5-(3-fluoromethoxyphenyl)-2-pyrimidinyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(85) trans-3-oxo-N-(6-phenyl-1,2,4-triazin-3-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(86) trans-N-[5-(2-difluoromethoxyphenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(87) trans-N-[5-(3-difluoromethoxyphenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(88) trans-N-[5-(3-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(89) trans-N-[5-(4-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(90) trans-N-(4-benzoylphenyl)-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(91) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(92) trans-3-oxo-N-[2-phenyl-4-pyridyl]spiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(93) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(94) trans-3-oxo-N-(1-phenyl-3-pyrrolyl)spiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(95) trans-N-[1-(4-fluorophenyl)-3-pyrazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(96) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(97) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(98) trans-N-[1-(3-fluorophenyl)-4-pyrazolyl]-3-oxospiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(99) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(100) trans-N-[1-(4-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(101) trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(102) trans-3-oxo-N-(5-phenyl-1,2,4-thiadiazol-3-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(103) trans-3-oxo-N-(5-phenyl-3-isoxazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(104) trans-3-oxo-N-(6-phenyl-3-pyridyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(105) trans-3-oxo-N-(2-phenyl-3-thiazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(107) trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

and pharmaceutically acceptable salts and esters thereof.

14. The composition of Claim 13 wherein the NPY5 antagonist is selected from the group consisting of

(1) 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(2) 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(3) N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(4) trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(5) trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(7) trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(8) trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(9) trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(10) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(11) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(12) trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

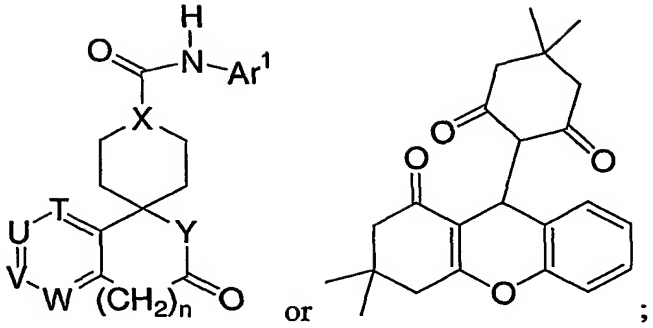
(13) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; and

(14) trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

and pharmaceutically acceptable salts and esters thereof.

15. A composition comprising

(a) a NPY5 antagonist of formula I or II



(I)

or

(II)

;

and pharmaceutically acceptable salts and esters thereof, wherein

Ar^1 is selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein the aryl and heteroaryl groups are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,

(b) nitro,

(c) lower alkyl,

(d) halo(lower)alkyl,

(e) hydroxy(lower)alkyl,

(f) cyclo(lower)alkyl,

(g) lower alkenyl,

(h) lower alkoxy,

(i) halo(lower)alkoxy,

(j) lower alkylthio,

(k) carboxyl,

(l) lower alkanoyl,

(m) lower alkoxycarbonyl,

(n) lower alkylene optionally substituted with oxo, and

(o) -Q-Ar^2;

Ar^2 is selected from the group consisting of

(1) aryl, and

(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,
(b) cyano,
(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) hydroxy,
(g) lower alkoxy,
(h) halo(lower)alkoxy,
(i) lower alkylamino,
(j) di-lower alkylamino,
(k) lower alkanoyl, and
(l) aryl;

n is 0 or 1;

Q is selected from the group consisting of a single bond or carbonyl;

T, U, V and W are each independently selected from the group consisting of

(1) nitrogen, and
(2) methine,

wherein the methine group is unsubstituted or optionally substituted with a substituent selected from the group consisting of

(a) halogen,
(b) lower alkyl,
(c) hydroxy, and
(d) lower alkoxy, and

wherein at least two of T, U, V, and W are methine;

X is selected from the group consisting of

(1) nitrogen, and
(2) methine; and

Y is selected from the group consisting of

(1) imino, unsubstituted or optionally substituted with lower alkyl, and
(2) oxygen; and

(b) an anti-obesity agent selected from the group consisting of:

(1) aminorex;
(2) amphechloral;
(3) amphetamine;
(4) benzphetamine;
(5) chlorphentermine;
(6) clobenzorex;
(7) cloforex;
(8) clominorex;
(9) clortermine;
(10) cyclexedrine;
(11) dexfenfluramine;
(12) dextroamphetamine;
(13) diethylpropion;
(14) diphemethoxidine,
(15) N-ethylamphetamine;
(16) fenbutrazate;
(17) fenfluramine;
(18) fenisorex;
(19) fenproporex;
(20) fludorex;
(21) fluminorex;
(22) furfurylmethylamphetamine;
(23) levamfetamine;
(24) levophacetoperane;
(25) mazindol;
(26) mefenorex;
(27) metamfepramone;
(28) methamphetamine;
(29) norpseudoephedrine;
(30) pentorex;
(31) phendimetrazine;
(32) phenmetrazine;
(33) phentermine;
(34) phenylpropanolamine; and

(35) picilorex;

and pharmaceutically acceptable salts thereof.

16. A composition comprising

(a) a NPY5 antagonist selected from the group consisting of:

(1) 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(2) 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(3) N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(4) trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(5) trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(6) trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(7) trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(8) trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(9) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(10) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(12) trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(13) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; and

(14) trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

and pharmaceutically acceptable salts and esters thereof; and

(b) a Mc4r agonist selected from the group consisting of:

(1) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chloro phenyl]-N-methylcarboxamide;

(2) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluoro-phenyl]-N-methylcarboxamide;

(3) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-methyl-phenyl]-N-methylcarboxamide;

(4) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-phenyl]-N-methylcarboxamide;

(5) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-methyl-phenyl]-N-methylcarboxamide;

(6) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-fluoro-phenyl]-N-methylcarboxamide;

(7) 4-[2-(2-azetidin-1-yl-1(S)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(8) 4-[2-(2-azetidin-1-yl-1(R)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(9) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(10) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(11) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(12) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(13) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(14) N-{(1R)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(15) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-1-methylethyl}acetamide;

(16) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(17) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}cyclobutanecarboxamide;

(18) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}propanamide;

(19) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}-*N*-methylurea;

(20) Methyl-2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-2-methylpropanoate;

(21) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]-1-methylethyl}acetamide;

(22) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}-*N*-methylurea;

(23) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}cyclobutanecarboxamide;

(24) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}propanamide;

(25) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(26) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]propyl}acetamide; and

(27) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}pyrimidine-5-carboxamide;

and pharmaceutically acceptable salts thereof.

17. A composition comprising

(a) a NPY5 antagonist selected from the group consisting of:

(1) 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(2) 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(3) N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(4) trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(5) trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(6) trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(7) trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(8) trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(9) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(10) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(11) trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(12) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; and

(13) trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

and pharmaceutically acceptable salts and esters thereof; and

(b) a Mc4r agonist selected from the group consisting of:

(1) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide,

(2) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]propyl}acetamide,

(3) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide, ,

(4) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chloro phenyl]-N-methylcarboxamide,

(5) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}pyrimidine-5-carboxamide, and

(6) 4-[2-(2-azetidin-1-yl-1(S)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine,

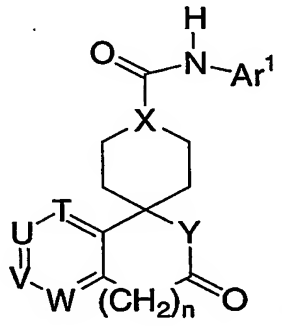
and pharmaceutically acceptable salts thereof.

18. A composition according to Claim 1 further comprising a pharmaceutically acceptable carrier.

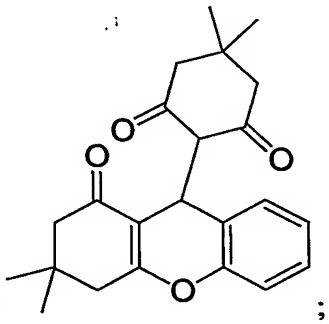
19. A composition according to Claim 13 further comprising a pharmaceutically acceptable carrier.

20. A composition according to Claim 16 or 17 further comprising a pharmaceutically acceptable carrier.

21. A method of preventing obesity in a subject at risk for obesity comprising administration to said subject
(a) a prophylactically effective amount of a NPY5 antagonist of Formula I or II:



or



;

(I)

(II)

and pharmaceutically acceptable salts and esters thereof, wherein
Ar^1 is selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein the aryl and heteroaryl groups are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,

(b) nitro,

(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) cyclo(lower)alkyl,
(g) lower alkenyl,
(h) lower alkoxy,
(i) halo(lower)alkoxy,
(j) lower alkylthio,
(k) carboxyl,
(l) lower alkanoyl,
(m) lower alkoxycarbonyl,
(n) lower alkylene optionally substituted with oxo, and
(o) -Q-Ar^2;

Ar^2 is selected from the group consisting of
(1) aryl, and
(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or optionally substituted with a substituent selected from the group consisting of:
(a) halogen,
(b) cyano,
(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) hydroxy,
(g) lower alkoxy,
(h) halo(lower)alkoxy,
(i) lower alkylamino,
(j) di-lower alkylamino,
(k) lower alkanoyl, and
(l) aryl;

n is 0 or 1;

Q is selected from the group consisting of a single bond or carbonyl;

T, U, V and W are each independently selected from the group consisting of
(1) nitrogen, and

(2) methine,

wherein the methine group is unsubstituted or optionally substituted with a substituent selected from the group consisting of

(a) halogen,

(b) lower alkyl,

(c) hydroxy, and

(d) lower alkoxy, and

wherein at least two of T, U, V, and W are methine;

X is selected from the group consisting of

(1) nitrogen, and

(2) methine; and

Y is selected from the group consisting of

(1) imino, unsubstituted or optionally substituted with lower alkyl, and

(2) oxygen; and

(b) a prophylactically effective amount of an anti-obesity agent selected from the group consisting of:

(1) 5HT transporter inhibitor;

(2) NE transporter inhibitor;

(3) CB-1 antagonist/inverse agonist;

(4) Ghrelin antagonist;

(5) H3 antagonist/inverse agonist;

(6) MCH1R antagonist;

(7) MCH2R agonist/antagonist;

(8) NPY1 antagonist;

(9) leptin;

(10) leptin derivatives;

(11) opioid antagonist;

(12) orexin antagonist;

(13) BRS3 agonist;

(14) CCK-A agonist;

(15) CNTF;

(16) CNTF derivatives;

(17) GHS agonist;

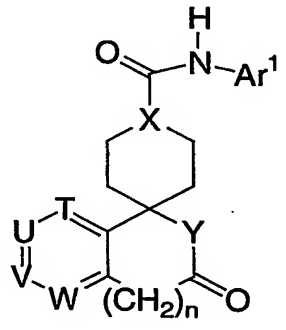
(18) 5HT2C agonist;

(19) monoamine reuptake inhibitor;
(20) UCP-1, 2, and 3 activator;
(21) β3 agonist;
(22) thyroid hormone β agonist;
(23) PDE inhibitor;
(24) FAS inhibitor;
(25) DGAT1 inhibitor;
(26) DGAT2 inhibitor;
(27) ACC2 inhibitor;
(28) glucocorticoid antagonist;
(29) acyl-estrogens;
(30) lipase inhibitor;
(31) fatty acid transporter inhibitor;
(32) dicarboxylate transporter inhibitor;
(33) glucose transporter inhibitor;
(34) serotonin reuptake inhibitors;
(35) metformin; and
(36) topiramate;

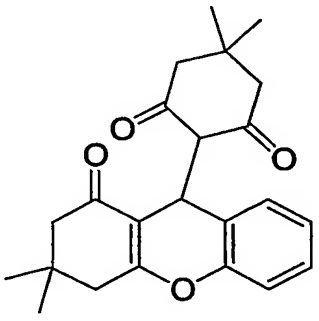
and pharmaceutically acceptable salts and esters thereof.

22. The method of treating a subject having a disorder associated with excessive food intake comprising administration of

(a) a therapeutically effective amount of a NPY5 antagonist of Formula I or II:



or



;

(I)

(II)

and pharmaceutically acceptable salts and esters thereof, wherein

Ar^1 is selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein the aryl and heteroaryl groups are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,

(b) nitro,

(c) lower alkyl,

(d) halo(lower)alkyl,

(e) hydroxy(lower)alkyl,

(f) cyclo(lower)alkyl,

(g) lower alkenyl,

(h) lower alkoxy,

(i) halo(lower)alkoxy,

(j) lower alkylthio,

(k) carboxyl,

(l) lower alkanoyl,

(m) lower alkoxycarbonyl,

(n) lower alkylene optionally substituted with oxo, and

(o) -Q-Ar^2;

Ar^2 is selected from the group consisting of

(1) aryl, and

(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,

(b) cyano,

(c) lower alkyl,

(d) halo(lower)alkyl,

(e) hydroxy(lower)alkyl,

(f) hydroxy,

(g) lower alkoxy,

(h) halo(lower)alkoxy,
(i) lower alkylamino,
(j) di-lower alkylamino,
(k) lower alkanoyl, and
(l) aryl;

n is 0 or 1;

Q is selected from the group consisting of a single bond or carbonyl;

T, U, V and W are each independently selected from the group consisting of
(1) nitrogen, and
(2) methine,
wherein the methine group is unsubstituted or optionally substituted with a substituent selected from the group consisting of
(a) halogen,
(b) lower alkyl,
(c) hydroxy, and
(d) lower alkoxy, and

wherein at least two of T, U, V, and W are methine;

X is selected from the group consisting of
(1) nitrogen, and
(2) methine; and

Y is selected from the group consisting of
(1) imino, unsubstituted or optionally substituted with lower alkyl, and
(2) oxygen; and

(b) a therapeutically effective amount of an anti-obesity agent selected from the group consisting of:
(1) 5HT transporter inhibitor;
(2) NE transporter inhibitor;
(3) CB-1 antagonist/inverse agonist;
(4) Ghrelin antagonist;
(5) H3 antagonist/inverse agonist;
(6) MCH1R antagonist;
(7) MCH2R agonist/antagonist;
(8) NPY1 antagonist;
(9) leptin;

(10) leptin derivatives;
(11) opioid antagonist;
(12) orexin antagonist;
(13) BRS3 agonist;
(14) CCK-A agonist;
(15) CNTF;
(16) CNTF derivatives;
(17) GHS agonist;
(18) 5HT2C agonist;
(19) monoamine reuptake inhibitor;
(20) UCP-1, 2, and 3 activator;
(21) β3 agonist;
(22) thyroid hormone β agonist;
(23) PDE inhibitor;
(24) FAS inhibitor;
(25) DGAT1 inhibitor;
(26) DGAT2 inhibitor;
(27) ACC2 inhibitor;
(28) glucocorticoid antagonist;
(29) acyl-estrogens;
(30) lipase inhibitor;
(31) fatty acid transporter inhibitor;
(32) dicarboxylate transporter inhibitor;
(33) glucose transporter inhibitor;
(34) serotonin reuptake inhibitors;
(35) metformin; and
(36) topiramate;

and pharmaceutically acceptable salts and esters thereof;
to a subject in need of such treatment.

23. The method according to Claim 22 wherein the disorder associated with excessive food intake is obesity.

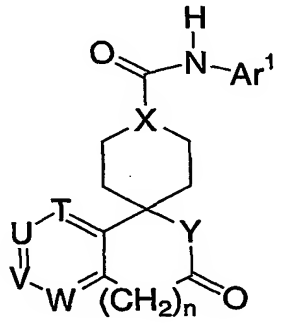
24. A method according to Claim 22 wherein the disorder associated with excessive food intake is an obesity-related disorder.

25. The method according to Claim 24 wherein the obesity-related disorder is selected from: overeating; bulimia; hypertension; diabetes, elevated plasma insulin concentrations; insulin resistance; dyslipidemia; hyperlipidemia; endometrial, breast, prostate and colon cancer; osteoarthritis; obstructive sleep apnea; cholelithiasis; gallstones; coronary heart disease; abnormal heart rhythms; heart arrythmias; myocardial infarction; polycystic ovarian disease; craniopharyngioma; the Prader-Willi Syndrome; Frohlich's syndrome; GH-deficient subjects; normal variant short stature; Turner's syndrome; and acute lymphoblastic leukemia.

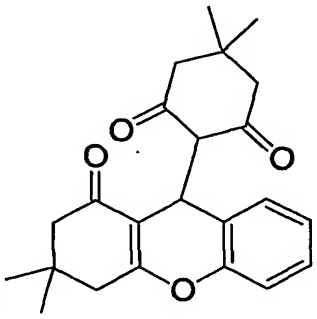
26. The method according to Claim 25 wherein the obesity-related disorder is diabetes.

27. The use of

(a) a therapeutically effective amount of a NPY5 antagonist of Formula I or II:



or



;

(I)

(II)

and pharmaceutically acceptable salts and esters thereof, wherein

Ar^1 is selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein the aryl and heteroaryl groups are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,
(b) nitro,
(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) cyclo(lower)alkyl,
(g) lower alkenyl,
(h) lower alkoxy,
(i) halo(lower)alkoxy,
(j) lower alkylthio,
(k) carboxyl,
(l) lower alkanoyl,
(m) lower alkoxycarbonyl,
(n) lower alkylene optionally substituted with oxo, and
(o) -Q-Ar^2;

Ar^2 is selected from the group consisting of

(1) aryl, and
(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,
(b) cyano,
(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) hydroxy,
(g) lower alkoxy,
(h) halo(lower)alkoxy,
(i) lower alkylamino,
(j) di-lower alkylamino,
(k) lower alkanoyl, and
(l) aryl;

n is 0 or 1;

Q is selected from the group consisting of a single bond or carbonyl;

T, U, V and W are each independently selected from the group consisting of

(1) nitrogen, and

(2) methine,

wherein the methine group is unsubstituted or optionally substituted with a substituent selected from the group consisting of

(a) halogen,

(b) lower alkyl,

(c) hydroxy, and

(d) lower alkoxy, and

wherein at least two of T, U, V, and W are methine;

X is selected from the group consisting of

(1) nitrogen, and

(2) methine; and

Y is selected from the group consisting of

(1) imino, unsubstituted or optionally substituted with lower alkyl, and

(2) oxygen; and

(b) a therapeutically effective amount of an anti-obesity agent selected from the group consisting of:

(1) 5HT transporter inhibitor;

(2) NE transporter inhibitor;

(3) CB-1 antagonist/inverse agonist;

(4) Ghrelin antagonist;

(5) H3 antagonist/inverse agonist;

(6) MCH1R antagonist;

(7) MCH2R agonist/antagonist;

(8) NPY1 antagonist;

(9) leptin;

(10) leptin derivatives;

(11) opioid antagonist;

(12) orexin antagonist;

(13) BRS3 agonist;

(14) CCK-A agonist;

(15) CNTF;
(16) CNTF derivatives;
(17) GHS agonist;
(18) 5HT2C agonist;
(19) monoamine reuptake inhibitor;
(20) UCP-1, 2, and 3 activator;
(21) β3 agonist;
(22) thyroid hormone β agonist;
(23) PDE inhibitor;
(24) FAS inhibitor;
(25) DGAT1 inhibitor;
(26) DGAT2 inhibitor;
(27) ACC2 inhibitor;
(28) glucocorticoid antagonist;
(29) acyl-estrogens;
(30) lipase inhibitor;
(31) fatty acid transporter inhibitor;
(32) dicarboxylate transporter inhibitor;
(33) glucose transporter inhibitor;
(34) serotonin reuptake inhibitors;
(35) metformin; and
(36) topiramate;

for the manufacture of a medicament useful for the treatment of a disorder associated with excessive food intake in a subject in need of such treatment.

28. The use according to Claim 27 wherein the disorder associated with excessive food intake is obesity.

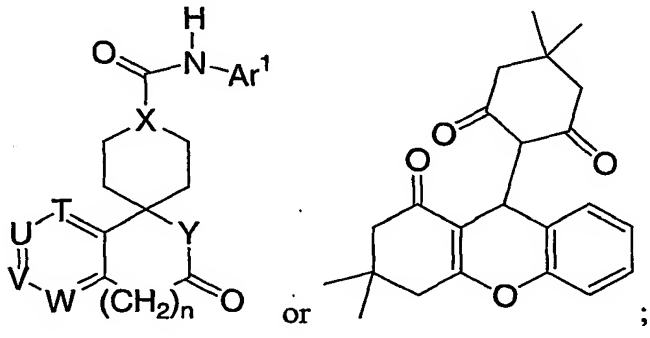
29. The use according to Claim 27 wherein the disorder associated with excessive food intake is an obesity-related disorder.

30. The use according to Claim 29 wherein the obesity-related disorder is selected from: overeating; bulimia; hypertension; diabetes, elevated plasma insulin concentrations; insulin resistance; dyslipidemia; hyperlipidemia;

endometrial, breast, prostate and colon cancer; osteoarthritis; obstructive sleep apnea; cholelithiasis; gallstones; coronary heart disease; abnormal heart rhythms; heart arrythmias; myocardial infarction; polycystic ovarian disease; craniopharyngioma; the Prader-Willi Syndrome; Frohlich's syndrome; GH-deficient subjects; normal variant short stature; Turner's syndrome; and acute lymphoblastic leukemia.

31. The use according to Claim 30 wherein the obesity-related disorder is diabetes.

32. The use of an NPY5 antagonist of Formula I or II



(I) (II)

and pharmaceutically acceptable salts and esters thereof, wherein

Ar^1 is selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein the aryl and heteroaryl groups are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,

(b) nitro,

(c) lower alkyl,

(d) halo(lower)alkyl,

(e) hydroxy(lower)alkyl,

(f) cyclo(lower)alkyl,

(g) lower alkenyl,
(h) lower alkoxy,
(i) halo(lower)alkoxy,
(j) lower alkylthio,
(k) carboxyl,
(l) lower alkanoyl,
(m) lower alkoxycarbonyl,
(n) lower alkylene optionally substituted with oxo, and
(o) -Q-Ar^2;

Ar^2 is selected from the group consisting of
(1) aryl, and
(2) heteroaryl,
wherein aryl and heteroaryl are unsubstituted or optionally substituted with a substituent selected from the group consisting of:
(a) halogen,
(b) cyano,
(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) hydroxy,
(g) lower alkoxy,
(h) halo(lower)alkoxy,
(i) lower alkylamino,
(j) di-lower alkylamino,
(k) lower alkanoyl, and
(l) aryl;

n is 0 or 1;
Q is selected from the group consisting of a single bond or carbonyl;
T, U, V and W are each independently selected from the group consisting of
(1) nitrogen, and
(2) methine,
wherein the methine group is unsubstituted or optionally substituted with a substituent selected from the group consisting of
(a) halogen,

(b) lower alkyl,

(c) hydroxy, and

(d) lower alkoxy, and

wherein at least two of T, U, V, and W are methine;

X is selected from the group consisting of

(1) nitrogen, and

(2) methine; and

Y is selected from the group consisting of

(1) imino, unsubstituted or optionally substituted with lower alkyl, and

(2) oxygen;

and an anti-obesity agent selected from the group consisting of:

(1) 5HT transporter inhibitor;

(2) NE transporter inhibitor;

(3) CB-1 antagonist/inverse agonist;

(4) Ghrelin antagonist;

(5) H3 antagonist/inverse agonist;

(6) MCH1R antagonist;

(7) MCH2R agonist/antagonist;

(8) NPY1 antagonist;

(9) leptin;

(10) leptin derivatives;

(11) opioid antagonist;

(12) orexin antagonist;

(13) BRS3 agonist;

(14) CCK-A agonist;

(15) CNTF;

(16) CNTF derivatives;

(17) GHS agonist;

(18) 5HT2C agonist;

(19) monoamine reuptake inhibitor;

(20) UCP-1, 2, and 3 activator;

(21) β3 agonist;

(22) thyroid hormone β agonist;

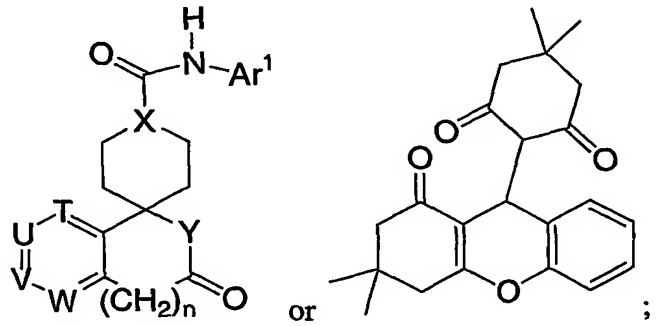
(23) PDE inhibitor;

(24) FAS inhibitor;
(25) DGAT1 inhibitor;
(26) DGAT2 inhibitor;
(27) ACC2 inhibitor;
(28) glucocorticoid antagonist;
(29) acyl-estrogens;
(30) lipase inhibitor;
(31) fatty acid transporter inhibitor;
(32) dicarboxylate transporter inhibitor;
(33) glucose transporter inhibitor;
(34) serotonin reuptake inhibitors;
(35) metformin; and
(36) topiramate;

and pharmaceutically acceptable salts and esters thereof;

for the manufacture of a medicament for treatment of obesity which comprises an effective amount of NPY5 antagonist of Formula I or II and an effective amount of anti-obesity agent, together or separately.

33. A product containing a NPY5 antagonist of Formula I or II



(I)

or

(II)

;

and pharmaceutically acceptable salts and esters thereof, wherein

Ar^1 is selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein the aryl and heteroaryl groups are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,
(b) nitro,
(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) cyclo(lower)alkyl,
(g) lower alkenyl,
(h) lower alkoxy,
(i) halo(lower)alkoxy,
(j) lower alkylthio,
(k) carboxyl,
(l) lower alkanoyl,
(m) lower alkoxycarbonyl,
(n) lower alkylene optionally substituted with oxo, and
(o) -Q-Ar^2;

Ar^2 is selected from the group consisting of

(1) aryl, and
(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,
(b) cyano,
(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) hydroxy,
(g) lower alkoxy,
(h) halo(lower)alkoxy,
(i) lower alkylamino,
(j) di-lower alkylamino,
(k) lower alkanoyl, and

(l) aryl;

n is 0 or 1;

Q is selected from the group consisting of a single bond or carbonyl;

T, U, V and W are each independently selected from the group consisting of

(1) nitrogen, and

(2) methine,

wherein the methine group is unsubstituted or optionally substituted with a substituent selected from the group consisting of

(a) halogen,

(b) lower alkyl,

(c) hydroxy, and

(d) lower alkoxy, and

wherein at least two of T, U, V, and W are methine;

X is selected from the group consisting of

(1) nitrogen, and

(2) methine; and

Y is selected from the group consisting of

(1) imino, unsubstituted or optionally substituted with lower alkyl, and

(2) oxygen;

and an anti-obesity agent selected from the group consisting of:

(1) 5HT transporter inhibitor;

(2) NE transporter inhibitor;

(3) CB-1 antagonist/inverse agonist;

(4) Ghrelin antagonist;

(5) H3 antagonist/inverse agonist;

(6) MCH1R antagonist;

(7) MCH2R agonist/antagonist;

(8) NPY1 antagonist;

(9) leptin;

(10) leptin derivatives;

(11) opioid antagonist;

(12) orexin antagonist;

(13) BRS3 agonist;

(14) CCK-A agonist;

(15) CNTF;
(16) CNTF derivatives;
(17) GHS agonist;
(18) 5HT2C agonist;
(19) monoamine reuptake inhibitor;
(20) UCP-1, 2, and 3 activator;
(21) β3 agonist;
(22) thyroid hormone β agonist;
(23) PDE inhibitor;
(24) FAS inhibitor;
(25) DGAT1 inhibitor;
(26) DGAT2 inhibitor;
(27) ACC2 inhibitor;
(28) glucocorticoid antagonist;
(29) acyl-estrogens;
(30) lipase inhibitor;
(31) fatty acid transporter inhibitor;
(32) dicarboxylate transporter inhibitor;
(33) glucose transporter inhibitor;
(34) serotonin reuptake inhibitors;
(35) metformin; and
(36) topiramate;

and pharmaceutically acceptable salts and esters thereof;
as a combined preparation for simultaneous, separate or sequential use in obesity.

34. A method of preventing obesity in a subject at risk for obesity comprising administration to said subject
(a) a prophylactically effective amount of a NPY5 antagonist selected from the group consisting of:

(1) 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(2) 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(3) N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(4) trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(5) trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(6) trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(7) trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(8) trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(9) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(10) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(11) trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(12) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; and

(13) trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

and pharmaceutically acceptable salts and esters thereof; and

(b) a prophylactically effective amount of a Mc4r agonist selected from the group consisting of:

(1) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chloro phenyl]-N-methylcarboxamide;

(2) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluoro-phenyl]-N-methylcarboxamide;

(3) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-methyl-phenyl]-N-methylcarboxamide;

(4) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-phenyl]-N-methylcarboxamide;

(5) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-methyl-phenyl]-N-methylcarboxamide;

(6) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-fluoro-phenyl]-N-methylcarboxamide;

(7) 4-[2-(2-azetidin-1-yl-1(S)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(8) 4-[2-(2-azetidin-1-yl-1(R)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(9) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(10) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(11) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(12) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(13) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(14) N-{(1R)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(15) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-1-methylethyl}acetamide;

(16) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(17) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}cyclobutanecarboxamide;

(18) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}propanamide;

(19) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}-*N*-methylurea;

(20) Methyl-2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-2-methylpropanoate;

(21) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]-1-methylethyl}acetamide;

(22) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}-*N*-methylurea;

(23) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}cyclobutanecarboxamide;

(24) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}propanamide;

(25) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(26) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]propyl}acetamide; and

(27) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}pyrimidine-5-carboxamide;

and pharmaceutically acceptable salts thereof.

35. The method of treating a subject having a disorder associated with excessive food intake comprising administration of

(a) a therapeutically effective amount of a NPY5 antagonist selected from the group consisting of:

(1) 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(2) 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(3) N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(4) trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(5) trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(6) trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(7) trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(8) trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(9) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(10) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(11) trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(12) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; and

(13) trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

and pharmaceutically acceptable salts and esters thereof; and

(b) a therapeutically effective amount of a Mc4r agonist selected from the group consisting of:

(1) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chloro phenyl]-N-methylcarboxamide;

(2) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluoro-phenyl]-N-methylcarboxamide;

(3) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-methyl-phenyl]-N-methylcarboxamide;

(4) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-phenyl]-N-methylcarboxamide;

(5) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-methyl-phenyl]-N-methylcarboxamide;

(6) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-fluoro-phenyl]-N-methylcarboxamide;

(7) 4-[2-(2-azetidin-1-yl-1(S)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(8) 4-[2-(2-azetidin-1-yl-1(R)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(9) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(10) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(11) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(12) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(13) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(14) N-{(1R)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(15) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-1-methylethyl}acetamide;

(16) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(17) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}cyclobutanecarboxamide;

(18) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}propanamide;

(19) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}-*N*-methylurea;

(20) Methyl-2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-2-methylpropanoate;

(21) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]-1-methylethyl}acetamide;

(22) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}-*N*-methylurea;

(23) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}cyclobutanecarboxamide;

(24) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}propanamide;

(25) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(26) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]propyl}acetamide; and

(27) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}pyrimidine-5-carboxamide;

and pharmaceutically acceptable salts thereof;

to a subject in need of such treatment.

36. The method according to Claim 35 wherein the disorder associated with excessive food intake is obesity.

37. A method according to Claim 35 wherein the disorder associated with excessive food intake is an obesity-related disorder.

38. The method according to Claim 37 wherein the obesity-related disorder is selected from: overeating; bulimia; hypertension; diabetes, elevated plasma insulin concentrations; insulin resistance; dyslipidemia; hyperlipidemia; endometrial, breast, prostate and colon cancer; osteoarthritis; obstructive sleep apnea; cholelithiasis; gallstones; coronary heart disease; abnormal heart rhythms; heart arrythmias; myocardial infarction; polycystic ovarian disease; craniopharyngioma; the Prader-Willi Syndrome; Frohlich's syndrome; GH-deficient subjects; normal variant short stature; Turner's syndrome; and acute lymphoblastic leukemia.

39. The method according to Claim 38 wherein the obesity-related disorder is diabetes.

40. The use of

(a) a therapeutically effective amount of a NPY5 antagonist selected from the group consisting of:

(1) 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(2) 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(3) N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(4) trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(5) trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(6) trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(7) trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(8) trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(9) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(10) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(11) trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(12) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; and

(13) trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

and pharmaceutically acceptable salts and esters thereof; and

(b) a therapeutically effective amount of a Mc4r agonist selected from the group consisting of:

(1) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chloro phenyl]-N-methylcarboxamide;

(2) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluoro-phenyl]-N-methylcarboxamide;

(3) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-methyl-phenyl]-N-methylcarboxamide;

(4) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-phenyl]-N-methylcarboxamide;

(5) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-methyl-phenyl]-N-methylcarboxamide;

(6) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-fluoro-phenyl]-N-methylcarboxamide;

(7) 4-[2-(2-azetidin-1-yl-1(S)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(8) 4-[2-(2-azetidin-1-yl-1(R)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(9) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(10) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(11) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(12) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(13) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(14) N-{(1R)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(15) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-1-methylethyl}acetamide;

(16) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(17) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}cyclobutanecarboxamide;

(18) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}propanamide;

(19) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}-*N*-methylurea;

(20) Methyl-2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-2-methylpropanoate;

(21) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]-1-methylethyl}acetamide;

(22) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}-*N*-methylurea;

(23) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}cyclobutanecarboxamide;

(24) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}propanamide;

(25) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(26) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]propyl}acetamide; and

(27) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}pyrimidine-5-carboxamide;

and pharmaceutically acceptable salts and esters thereof;

for the manufacture of a medicament useful for the treatment of a disorder associated with excessive food intake in a subject in need of such treatment.

41. The use according to Claim 40 wherein the disorder associated with excessive food intake is obesity.

42. The use according to Claim 40 wherein the disorder associated with excessive food intake is an obesity-related disorder.

43. The use according to Claim 42 wherein the obesity-related disorder is selected from: overeating; bulimia; hypertension; diabetes, elevated plasma insulin concentrations; insulin resistance; dyslipidemia; hyperlipidemia; endometrial, breast, prostate and colon cancer; osteoarthritis; obstructive sleep apnea; cholelithiasis; gallstones; coronary heart disease; abnormal heart rhythms; heart arrythmias; myocardial infarction; polycystic ovarian disease; craniopharyngioma; the Prader-Willi Syndrome; Frohlich's syndrome; GH-deficient subjects; normal variant short stature; Turner's syndrome; and acute lymphoblastic leukemia.

44. The use according to Claim 43 wherein the obesity-related disorder is diabetes.

45. The use of an NPY5 antagonist selected from the group

consisting of

(1) 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(2) 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(3) N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(4) trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(5) trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(6) trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(7) trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(8) trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(9) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(10) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(11) trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(12) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; and

(13) trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

and pharmaceutically acceptable salts and esters thereof;

and a Mc4r agonist selected from the group consisting of:

(1) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chloro phenyl]-N-methylcarboxamide;

(2) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluoro-phenyl]-N-methylcarboxamide;

(3) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-methyl-phenyl]-N-methylcarboxamide;

(4) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-phenyl]-N-methylcarboxamide;

(5) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-methyl-phenyl]-N-methylcarboxamide;

(6) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-fluoro-phenyl]-N-methylcarboxamide;

(7) 4-[2-(2-azetidin-1-yl-1(S)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(8) 4-[2-(2-azetidin-1-yl-1(R)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(9) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(10) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(11) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(12) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(13) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(14) N-{(1R)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(15) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-1-methylethyl}acetamide;

(16) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(17) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}cyclobutanecarboxamide;

(18) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}propanamide;

(19) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}-*N*-methylurea;

(20) Methyl-2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-2-methylpropanoate;

(21) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]-1-methylethyl}acetamide;

(22) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}-*N*-methylurea;

(23) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}cyclobutanecarboxamide;

(24) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}propanamide;

(25) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(26) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]propyl}acetamide; and

(27) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}pyrimidine-5-carboxamide;

and pharmaceutically acceptable salts and esters thereof;

for the manufacture of a medicament for treatment of obesity which comprises an effective amount of the NPY5 antagonist and an effective amount of the Mc4r agonist, together or separately.

46. A product containing a NPY5 antagonist selected from the group consisting of:

(1) 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(2) 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(3) N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide;

(4) trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(5) trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide;

(6) trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(7) trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(8) trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(9) trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(10) trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(11) trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

(12) trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; and

(13) trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide;

and pharmaceutically acceptable salts and esters thereof;

and a Mc4r agonist selected from the group consisting of:

(1) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chloro phenyl]-N-methylcarboxamide;

(2) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluoro-phenyl]-N-methylcarboxamide;

(3) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-methyl-phenyl]-N-methylcarboxamide;

(4) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-phenyl]-N-methylcarboxamide;

(5) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-methyl-phenyl]-N-methylcarboxamide;

(6) 2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl) pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-4-fluoro-phenyl]-N-methylcarboxamide;

(7) 4-[2-(2-azetidin-1-yl-1(S)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(8) 4-[2-(2-azetidin-1-yl-1(R)-methyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(9) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(10) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-chlorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(11) 4-[2-(2-azetidin-1-yl-1,1-dimethyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(12) 4-[2-(2-azetidin-1-yl-1-cyclopropyl-2-oxoethyl)-4-fluorophenyl]-1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidine;

(13) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(14) N-{(1R)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}acetamide;

(15) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-1-methylethyl}acetamide;

(16) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(17) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}cyclobutanecarboxamide;

(18) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}propanamide;

(19) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}-*N*-methylurea;

(20) Methyl-2-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]-2-methylpropanoate;

(21) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]-1-methylethyl}acetamide;

(22) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}-*N*-methylurea;

(23) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}cyclobutanecarboxamide;

(24) N-{1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluoro-phenyl)pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}propanamide;

(25) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-fluorophenyl]ethyl}acetamide;

(26) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]propyl}acetamide; and

(27) N-{(1S)-1-[2-(1-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)-pyrrolidin-3-yl]carbonyl}piperidin-4-yl)-5-chlorophenyl]ethyl}pyrimidine-5-carboxamide;

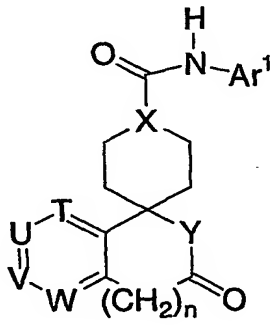
and pharmaceutically acceptable salts and esters thereof;

as a combined preparation for simultaneous, separate or sequential use in obesity.

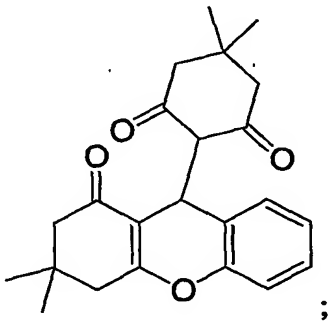
47. A kit comprising at least one unit dosage of a prophylactically or therapeutically effective amount of a NPY5 antagonist of Formula I or II, and pharmaceutically acceptable salts and esters thereof, and at least one unit dosage of a prophylactically or therapeutically effective amount of an anti-obesity agent, and pharmaceutically acceptable salts and esters thereof.

48. A method of maintaining weight loss in a subject comprising administration of

(a) a therapeutically effective amount of a NPY5 antagonist of Formula I or II:



or



;

(I)

(II)

and pharmaceutically acceptable salts and esters thereof, wherein

Ar^1 is selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein the aryl and heteroaryl groups are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,
(b) nitro,
(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) cyclo(lower)alkyl,
(g) lower alkenyl,
(h) lower alkoxy,
(i) halo(lower)alkoxy,
(j) lower alkylthio,
(k) carboxyl,
(l) lower alkanoyl,
(m) lower alkoxycarbonyl,
(n) lower alkylene optionally substituted with oxo, and
(o) -Q-Ar^2;

Ar^2 is selected from the group consisting of

(1) aryl, and
(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,
(b) cyano,
(c) lower alkyl,
(d) halo(lower)alkyl,
(e) hydroxy(lower)alkyl,
(f) hydroxy,
(g) lower alkoxy,
(h) halo(lower)alkoxy,
(i) lower alkylamino,
(j) di-lower alkylamino,
(k) lower alkanoyl, and
(l) aryl;

n is 0 or 1;

Q is selected from the group consisting of a single bond or carbonyl;

T, U, V and W are each independently selected from the group consisting of

(1) nitrogen, and

(2) methine,

wherein the methine group is unsubstituted or optionally substituted with a substituent selected from the group consisting of

(a) halogen,

(b) lower alkyl,

(c) hydroxy, and

(d) lower alkoxy, and

wherein at least two of T, U, V, and W are methine;

X is selected from the group consisting of

(1) nitrogen, and

(2) methine; and

Y is selected from the group consisting of

(1) imino, unsubstituted or optionally substituted with lower alkyl, and

(2) oxygen; and

(b) a therapeutically effective amount of an anti-obesity agent selected from the group consisting of:

(1) 5HT transporter inhibitor;

(2) NE transporter inhibitor;

(3) CB-1 antagonist/inverse agonist;

(4) Ghrelin antagonist;

(5) H3 antagonist/inverse agonist;

(6) MCH1R antagonist;

(7) MCH2R agonist/antagonist;

(8) NPY1 antagonist;

(9) leptin;

(10) leptin derivatives;

(11) opioid antagonist;

(12) orexin antagonist;

(13) BRS3 agonist;

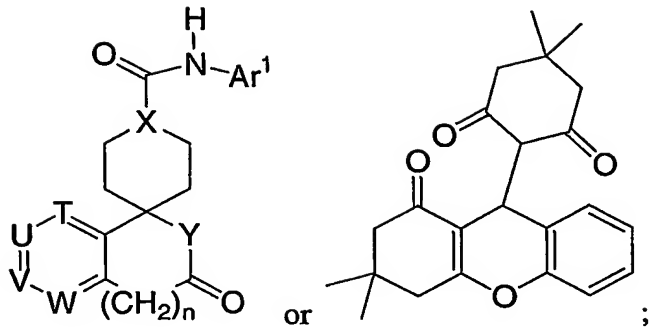
(14) CCK-A agonist;

(15) CNTF;
(16) CNTF derivatives;
(17) GHS agonist;
(18) 5HT2C agonist;
(19) monoamine reuptake inhibitor;
(20) UCP-1, 2, and 3 activator;
(21) β3 agonist;
(22) thyroid hormone β agonist;
(23) PDE inhibitor;
(24) FAS inhibitor;
(25) DGAT1 inhibitor;
(26) DGAT2 inhibitor;
(27) ACC2 inhibitor;
(28) glucocorticoid antagonist;
(29) acyl-estrogens;
(30) lipase inhibitor;
(31) fatty acid transporter inhibitor;
(32) dicarboxylate transporter inhibitor;
(33) glucose transporter inhibitor;
(34) serotonin reuptake inhibitors;
(35) metformin;
(36) topiramate;
(37) zonisamide;
(38) aminorex;
(39) amphechloral;
(40) amphetamine;
(41) benzphetamine;
(42) chlorphentermine;
(43) clobenzorex;
(44) cloforex;
(45) clominorex;
(46) clortermine;
(47) cyclexedrine;
(48) dexfenfluramine;

(49) dextroamphetamine;
(50) diethylpropion;
(51) diphemethoxidine,
(52) N-ethylamphetamine;
(53) fenbutrazate;
(54) fenfluramine;
(55) fenisorex;
(56) fenproporex;
(57) fludorex;
(58) fluminorex;
(59) furfurylmethylamphetamine;
(60) levamfetamine;
(61) levophacetoperane;
(62) mazindol;
(63) mefenorex;
(64) metamfepramone;
(65) methamphetamine;
(66) norpseudoephedrine;
(67) pentorex;
(68) phendimetrazine;
(69) phenmetrazine;
(70) phentermine;
(71) phenylpropanolamine; and
(72) picilorex;

and pharmaceutically acceptable salts and esters thereof;
to a subject in need of such treatment.

49. A composition comprising
(a) a NPY5 antagonist of formula I or II



(I) or (II);

and pharmaceutically acceptable salts and esters thereof, wherein

Ar^1 is selected from the group consisting of:

(1) aryl, and

(2) heteroaryl,

wherein the aryl and heteroaryl groups are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,

(b) nitro,

(c) lower alkyl,

(d) halo(lower)alkyl,

(e) hydroxy(lower)alkyl,

(f) cyclo(lower)alkyl,

(g) lower alkenyl,

(h) lower alkoxy,

(i) halo(lower)alkoxy,

(j) lower alkylthio,

(k) carboxyl,

(l) lower alkanoyl,

(m) lower alkoxycarbonyl,

(n) lower alkylene optionally substituted with oxo, and

(o) -Q-Ar^2;

Ar^2 is selected from the group consisting of

(1) aryl, and

(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or optionally substituted with a substituent selected from the group consisting of:

(a) halogen,

(b) cyano,

(c) lower alkyl,

(d) halo(lower)alkyl,

(e) hydroxy(lower)alkyl,

(f) hydroxy,

(g) lower alkoxy,

(h) halo(lower)alkoxy,

(i) lower alkylamino,

(j) di-lower alkylamino,

(k) lower alkanoyl, and

(l) aryl;

n is 0 or 1;

Q is selected from the group consisting of a single bond or carbonyl;

T, U, V and W are each independently selected from the group consisting of

(1) nitrogen, and

(2) methine,

wherein the methine group is unsubstituted or optionally substituted with a substituent selected from the group consisting of

(a) halogen,

(b) lower alkyl,

(c) hydroxy, and

(d) lower alkoxy, and

wherein at least two of T, U, V, and W are methine;

X is selected from the group consisting of

(1) nitrogen, and

(2) methine; and

Y is selected from the group consisting of

(1) imino, unsubstituted or optionally substituted with lower alkyl, and

(2) oxygen; and

(b) an anti-obesity agent selected from the group consisting of: zonisamide,

and pharmaceutically acceptable salts and esters thereof.

50. A method of treating a subject having a disorder associated with excessive food intake comprising administration of the composition of Claim 49 to a subject in need thereof.

51. The method according to Claim 50 wherein the disorder associated with excessive food intake is obesity.

52. A method according to Claim 51 wherein the disorder associated with excessive food intake is an obesity-related disorder.

53. The method according to Claim 52 wherein the obesity-related disorder is selected from: overeating; bulimia; hypertension; diabetes, elevated plasma insulin concentrations; insulin resistance; dyslipidemia; hyperlipidemia; endometrial, breast, prostate and colon cancer; osteoarthritis; obstructive sleep apnea; cholelithiasis; gallstones; coronary heart disease; abnormal heart rhythms; heart arrythmias; myocardial infarction; polycystic ovarian disease; craniopharyngioma; the Prader-Willi Syndrome; Frohlich's syndrome; GH-deficient subjects; normal variant short stature; Turner's syndrome; and acute lymphoblastic leukemia.

54. The method according to Claim 53 wherein the obesity-related disorder is diabetes.

55. A method of preventing obesity in a subject at risk for obesity comprising administration of the composition of claim 49 to said subject.